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Review

On the Modeling of Transcatheter Therapies for the Aortic and Mitral Valves: A Review

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Abstract: Transcatheter aortic valve replacement (TAVR) has become a milestone for the management of aortic stenosis in a growing number of patients who are unfavorable candidates for surgery. With the new generation of transcatheter heart valves (THV), the feasibility of transcatheter mitral valve replacement (TMVR) for degenerated mitral bioprostheses and failed annuloplasty rings has been demonstrated. In this setting, computational simulations are modernizing the preoperative planning of transcatheter heart valve interventions by predicting the outcome of the bioprosthesis interaction with the human host in a patient-specific fashion. However, computational modeling needs to carry out increasingly challenging levels including the verification and validation to obtain accurate and realistic predictions. This review aims to provide an overall assessment of the recent advances in computational modeling for TAVR and TMVR as well as gaps in the knowledge limiting model credibility and reliability.

Keywords: transcatheter aortic valve replacement; in silico model; computational fluid dynamics; transcatheter mitral valve replacement

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1. Introduction

Transcatheter valve interventions have transformed the management of valvular heart diseases as the outcome of patients with bioprosthetic devices is as favorable as that observed with porcine and mechanical heart valves. Current guidelines recommend transcatheter interventions in the elderly or patients with high surgical risk. Though surgery remains the best treatment option for patients between 50 and 60 years of age, the choice between transcatheter intervention and surgical repair remains controversial in patients suitable for both approaches.

As for the implantation of any device in the human body, the procedure outcome depends on the interaction between the host and the device in addition to the procedure variables. This device–host interaction has a fundamental role on the performance of transcatheter heart valves (THV), since the native valve leaflets are not excised in transcatheter therapies. Maladapting the THV device to the patient anatomy may lead to several acute complications such as paravalvular leakage, coronary obstruction in transcatheter aortic valve replacement (TAVR), as well as device protrusion in the left ventricle (namely, LVOT obstruction) and annulus rupture in the transcatheter mitral valve replacement (TMVR). These potential complications represent a clinical problem and are associated with impaired prognosis according to the patient baseline risk. It should also be considered that diagnostic imaging is the gold-standard approach to assessing the optimal device size for a remarkable number of valve technologies (i.e., self-expanding versus balloon-expandable THV). The selection of valve size and device type that best fits a given patient will play a key role in the outcome of TAVR; however, computer simulations have demonstrated the ability to predict the interaction between the human host and the device in TAVR.

Over the last few years, we have observed a substantial increase in the number of computational models of TAVR. Rigorous and realistic patient-specific computational models could potentially enhance the preprocedural planning to show different implantation scenarios and provide important insights in postprocedural care. Though an in-silico approach may reduce the need for clinical and animal trials, simulations must be carried out at an increasingly challenging level related to the need for verification and validation of the model output.

The objective of this review is to present the latest advances in computational simulations of TAVR and TMVR, with an emphasis on the clinical questions as well as the development for model verification and validation approaches. The PubMed and Scopus databases were adopted for manuscript selection using the following keywords: TAVR, TMVR, finite element analysis, computational fluid dynamics, and fluid–solid interaction.

2. TAVR

2.1. Clinical Background

Aortic valve stenosis (AS) is the most common degenerative heart valve disease and is associated with the occurrence of lipid accumulation followed by inflammation and calcification. The prevalence of patients with AS is estimated at 4.6% in patients ≥ 75 years and is expected to increase because of high life expectancy in the context of an aging population [1,2]. TAVR is recognized as an alternative and less invasive option to surgical aortic valve replacement (SAVR) for the elderly. However, long-term valve durability, the bicuspid aortic valve, and the long-term implications of conduction disturbances and permanent pacemaker implantation are the most common issues after TAVR [3–8]. TAVR remains a disservice in patients between 50 and 60 years of age.

According to the PARTNER 2 Trial [9], the rate of death in the TAVR group versus the SAVR group was similar in intermediate-risk patients, with patients undergoing TAVR having a low risk of stroke as compared to that of SAVR. The assessment of procedural risks is challenging and currently relies on the formulation of risk score systems, (i.e., the Society of Thoracic Surgeons (STS) score and the European System for Cardiac Operative Risk Evaluation (EuroSCORE) [10,11]. However, these score systems have poor predictive capability for quantifying the likelihood of TAVR-related mortality. Recently, the PARTNER 3 trial suggested low rates of death, stroke, and rehospitalization at 1 year, comparing balloon-expandable TAVR to surgery in low-risk patients [8]. The EVOLUT Low Risk trial showed that self-expanding TAVR was not inferior to surgery, with a low incidence of disabling stroke (4.1% vs. 4.3%), acute kidney injury, bleeding events, and atrial fibrillation but a high incidence of aortic regurgitation and permanent pacemaker implantation (17.4% vs. 6.1%) [12].

Individuals between 60 and 75 years of age, who have been only rarely included in TAVR trials, can be defined as "young" AS patients according to specific clinical characteristics. In this patient group, valve durability remains the major concern on the long-term clinical outcome with the hazard of multiple replacement procedures with aging. Moreover, severe AS on the bicuspid aortic valve is considered another patient group usually excluded by many clinical trials because of the risk of device elliptical expansion in the bicuspid annulus [3].

2.2. TAVR Simulation Background

Different simulation techniques including finite element analysis (FEA) and fluid–solid interaction (FSI) can be used to virtually deploy the bioprosthesis in patient-specific models. Once the deployment is simulated, structural and hemodynamic parameters related to the device–host interaction can be determined. Crimping is performed by gradually reducing the THV stent frame. Expansion is performed according to the valve technology including the expansion of a balloon placed coaxially to the balloon-expandable device or the gradual removal of the sleeve catheter to position the self-expandable THV.

The simulation starts with the anatomical segmentation of both the aortic root and calcified valve leaflets, followed by the modeling of the biomechanical tissue response (e.g., the mass and elastic material parameters), boundary conditions (e.g., the constraint from the subvalvular structure and the contact between the THV frame and aortic wall), the loading conditions (e.g., the level of balloon expansion), and the analysis options (e.g., the physics of the THV deployment). Once the solution is achieved, the deformed shape of the implanted bioprosthesis and the intramural stress exerted on the aortic wall can be quantitatively visualized to offer insights on the preoperative planning and, ultimately, on the likelihood of adverse complications.

Both computational fluid dynamics (CFD) and FSI are adopted to evaluate the post-TAVR hemodynamics. For CFD simulation, the deformed configuration resulting from the structural simulation of TAVR is adopted to perform the flow analysis using steady [13–16] or transient [17–19] analyses. The setup of CFD-related TAVR modeling is easy as compared to the FSI analysis, but the patient anatomy and device are considered rigid parts. Thus, the lack of deforming structure could be associated with unreliable outcomes. However, Bosi et al. [20] recently demonstrated that the aortic wall of patients undergoing TAVR is stiff and could be described with a linear elastic material model (i.e., a Young modulus of 4.5 MPa and a Poisson coefficient of 0.45) as compared to that of the healthy hyperelastic aorta. They also observed a small deformation of the aortic root when the bioprosthetic device was implanted, and this could justify the assumption of rigid aortic and device parts in CFD analyses of TAVR.

FSI overcomes the limit of rigid parts given the coupling of the fluid model with the structural solver, which is required to solve the dynamic motion of valve leaflets. Both Lagrangian-Eulerian and immersed boundary methods have been adopted. The Lagrangian-Eulerian method [18,21–23] needs two separated meshes for the fluid and the solid subdomain and is, therefore, challenging for a simulated TAVR procedure where valve leaflets are characterized by transient contact. The immersed boundary formulation presents the solid subdomain completely immersed in the fluid subdomain, resulting in a more suitable model for large structural deformations, thin elastic structures, and transient contact between structures [24]. Another numerical method is smoothed particle hydrodynamics (SPH), which uses a meshless approach to model the fluid domain [25–27]. The simplicity of SPH modelling as compared to that of the FSI technique is the use of the general contact algorithm to consider the interaction of the fluid with the structural domain. For the assessment of paravalvular leakage, the small gap between the bioprosthesis and the aortic wall may require a considerable amount of smoothed particles to obtain an accurate estimation of the flow velocity as reported by Pasta et al. [26].

Spatial discretization and material modeling are crucial for an accurate TAVR simulation. For a better understanding of modeling strategies, we recommend the recent review published by Luraghi et al. [28], who clearly described the impact of the aortic wall modeling (i.e., shell versus solid), tissue thickness, and constitutive models of each anatomical part on the resulting THV deployment. Recently, the Living Human Heart Model developed by Dassault Systems was also used to assess the deployment of the Evolut Pro THV in the setting of a stenotic aortic valve [29]. This cardiac tool is a realistic and high-fidelity model of an adult male heart, featuring the anatomy of the heart chambers, valves, and major vessels. The biomechanical response of the Living Human Heart Model is governed by realistic electrical, structural, and fluid flow physics, thereby representing the ideal cardiac tool to simulate TAVR and, thus, fully capture the interaction between the device and the human host in a beating heart. Ghosh and collaborators [18] modified the original anatomy of the Living Human Heart Model to incorporate the presence of calcific plaque and, then, investigated the effect of TAVR valve implantation depth on the valve anchorage and the resulting fluid mechanics. They also assessed the post-deployment thrombogenic potential of the Evolut Pro self-expanding device under different implan-

tation depths. The Living Human Heart Model could also represent a realistic tool to assess the impact of the metallic device frame on the heart electrophysiology; to the best of our knowledge, this aspect was not investigated.

2.3. Computational Model to Address Unmet Clinical Needs

2.3.1. Choice of the Device

In general, the bioprosthesis presents three biological leaflets mounted on a metallic stent frame partially covered by a sealing skirt. THVs are classified according to the expansion system in balloon-expandable versus self-expandable devices and are manufactured in different sizes to accommodate most of the aortic root anatomies [30]. The optimal device choice depends on several patient features including the annular diameter and morphology, the extent and distribution of calcification, the left ventricle outflow tract configuration, the height of the coronary ostium above the valve annulus, and the aortic angle [31,32]. Device sizing has a remarkable impact on the amount of radial forces exerted on the aortic wall. Indeed, inadequate radial forces could lead to paravalvular leakage and/or stent migration [33], while an excessive amount of radial expansion could cause cardiac conduction abnormalities or aortic rupture [34].

THVs have been accurately modeled in many studies simulating the TAVR procedure with the self-expandable CoreValve [15–19,35–38] and the balloon-expandable Sapien 3 [19,23,25,35]. Computational modeling has also been used to optimize the nitinol material properties used in self-expanding devices [13,39]. Specifically, material descriptors were obtained from the fitting of the stress–strain response as obtained by experimental radial force testing. There are, however, several numerical issues in TAVR simulations that need to be addressed. Indeed, none of current studies shows the crimping of the bioprosthesis upon the catheter diameter used in clinical practice. This is likely due to numerical issues resulting from distorted mesh elements when the crimping simulation reaches small diameter values. To avoid such numerical issues, researchers have partially modeled the crimping by stopping the simulation at a device diameter higher than the actual catheter diameter. Moreover, the presence of valve leaflets and the sealing skirt was not modeled in most of the computational studies. However, Bailey et al. [40] have clearly demonstrated that the bioprosthesis valve leaflets need to be considered in the simulation, because the tissue undergoes excessive stress and deformation that may compromise the device durability.

Comparing the Sapien 3 Ultra, Evolut Pro+, and Lotus is challenging because each device has unique features. The most relevant direct comparison demonstrated that the mortality rate was comparable between the Sapien 3 and Lotus devices, and that the incidence of pacemaker implantation with the Sapien 3 was similar to that of the Lotus device [41]. With regard to numerical simulations, Pasta and collaborators [27] found differences in the device performance of Sapien 3 versus the Evolut Pro THV devices, while Nappi et al. [42] revealed differences between the CoreValve and Sapien 3 THVs.

2.3.2. Paravalvular Leakage

Since the introduction of percutaneous procedures, paravalvular leakage (PVL) has been considered the "Achilles heel" of TAVR in several reports [43–45]. PVL leads to regurgitation during diastole because of the gap between the deployed valve and annulus. The gaps are subjected to large pressure gradients likely resulting in platelet activation and thrombus deposition and/or dissemination of emboli in the circulation, ultimately increasing the risk of stroke [19].

PVL can be predicted by the assessment of (i) incomplete prosthesis apposition to the native annulus, (ii) underexpansion, and (iii) the malpositioning of the device. [2,45] These risk factors could be partially predicted by means of pre-TAVR computed tomography (CT), which is pivotal in displaying the stenotic aortic valve [3]. A reduction in PVL has

been achieved by device design improvements as demonstrated by applications with the Sapien 3 Ultra or CoreValve EvolutProPlus devices [19].

Most of the computational analyses deal with the assessment of PVL from a structural and fluid dynamics perspective. The typical computational workflow first simulates the TAVR procedure and then performs the CFD or FSI to quantify PVL [14,16–20,23,25–27,35,36]. Among these, Mao et al. [17] found a good agreement between the predicted and echocardiographic-based measurements of PVL when simulating the CoreValve in patient-specific models. Similar studies have also demonstrated the capability of computational modeling to accurately predict the severity of PVL in patients with a bicuspid aortic valve [14,25,46].

2.3.3. Coronary Obstruction and Conduction Disturbances

Coronary obstruction is a rare but fatal complication after TAVR [47]. Wald et al. [22] provided a hemodynamic evaluation of TAVR cases in terms of the correlation between orifice area, systolic blood velocity, vortices location, pressure drop, and coronary flow using simplified 2D numerical simulations. They were able to accurately predict the risk of coronary obstruction as compared to clinical measurements. Recently, Heitkemper and collaborators [47] introduced the fractional obstruction index of a coronary obstruction with the goal of improving the risk prediction in patients undergoing TAVR.

New onset or worsening of conduction disturbances leading to permanent pacemaker implantation is one of the feared outcomes of TAVR. Among conduction disturbances, complete atrioventricular block, bundle branch block, and atrial fibrillation have been associated with TAVR. These complications result from the anatomical proximity of the device to the cardiac conduction system. Although PVL has been reduced with the new generation of THVs, a higher rate of conduction abnormalities (average rate of ~14.75%) was found with the Sapien 3 and CoreValve devices [48]. In this setting, McGee et al. [49] suggested a correlation between the numerically-predicted implantation depth of Lotus device and the onset of conduction disturbances. They found that the wall stress increased near the bundle of His, as a function of the implantation depth and conductance interference. Rocatello and collaborators [38] suggested that the risk of conduction abnormalities is linked to the contact pressure exerted by the THV stent frame on the aortic wall. Moreover, the Living Human Heart Model could play a central role in the assessment of electromechanical alteration of the cardiac tissue [29] given its capability of simulating cardiac electrophysiology coupled with biomechanical behavior. A synergic approach, integrating machine learning and computer simulation suggested a strong relationship between the insurgence of conduction abnormalities and/or pacemaker implantation with high rate of contact pressure [50].

2.3.4. Bicuspid Aortic Valve Patients

Although patients with a bicuspid aortic valve are excluded from all clinical trials, the clinical feasibility of TAVR in this complex patient population has been demonstrated [51,52]. The BAVARD (Bicuspid Aortic Valve Anatomy and Relationship with Devices) retrospective registry showed that patients with bicuspid anatomy of the aortic valve can experience prosthesis underexpansion, resulting in low prosthesis durability, aortic regurgitation, and leaflet thrombosis.

Patient-specific simulations have a central role in the evaluation of the interaction between the oval bicuspid annulus and the device performance [53]. Pasta et al. [25,26] used finite element analysis to evaluate the deformed configuration and contact pressure of Sapien 3 with the stenotic bicuspid valve. They also adopted the smoothed-particle hydrodynamic approach for the evaluation of PVL. The model predicted well the elliptical shape of the implanted THV frame as compared to that estimated by post-TAVR CT imaging. Similar studies modeled the deployment of THV devices in patients with bicuspid

anatomy of the aortic valve to assess the risk of PVL with the CoreValve device [14,16,46] and suggested the feasibility of TAVR in these patients.

3. TMVR

TMVR is usually performed to treat patients with multiple episodes of mitral valve failure, including the presence of a degenerated bioprosthesis (valve-in-valve), failed annuloplasty (valve-in-ring)m and mitral annular calcification (valve-in-MAC). Performing off-label TMVR with devices designed for TAVR represents a challenging procedure as the mitral valve has a unique annulus structure. The mitral apparatus is more complex and consists of valve leaflets, mitral annulus, papillary muscles, and chordae tendineae. Moreover, mitral valve physiology is characterized by a lower pressure state than that of the aortic valve.

THV implantation in the mitral position may lead to obstruction of the left ventricular outflow tract (LVOT) and annular rupture after TMVR. The LVOT consists of the basal septum anteriorly, the intervalvular fibrosa, and the anterior MV leaflet posteriorly. Device implantation in the mitral position leads to permanent displacement of the anterior MV leaflet towards the interventricular septum, thus resulting in an elongation of the outflow tract into the left ventricle. The newly created elongation is known as neo-LVOT and is a major concern for the TMVR procedure causing hemodynamic complications. A careful CT-based analysis of the patient anatomical suitability (i.e., left ventricular hypertrophy, unfavorable aorto–mitral angle, small ventricular cavity, and long anterior mitral leaflet) is the standard approach to exclude borderline anatomies and, thus, reduce the risk of adverse events [54]. Blanke et al. developed the idea of virtually implanting the THV in the patient anatomy for the assessment of the LVOT obstruction severity by evaluating the dimensions of neo-LVOT on CT images [55]. A few studies have highlighted the importance of 3D prototyping in the preprocedural assessment of TMVR. Evidence showed the advantage of 3D printed models in the assessment of PVL and optimal valve sizing [56,57].

Computer simulations have rarely been used to assess the risk of LVOT obstruction in TMVR. Using computational flow analysis, Kohli and collaborators [57] modeled the prolonged THV as a rigid wall protrusion in the left ventricle and observed an increase in the flow velocity and pressure drop across the neo-LVOT. Similarly, De Vecchi et al. [58] developed a parametric model of the protruded THV wall in the left ventricle and carried out several CFD analyses for different degrees of LVOT obstruction. They found a significant increase in the left ventricular afterload for maintaining the cardiac output and suggested a deterioration of systolic flow efficiency proportional to the degree of LVOT obstruction. However, these studies did not include the heart wall compliance or account for specific THV characteristics and deformed configurations. In a different way, Pasta et al. [59] simulated the left ventricular outflow tract (LVOT) obstruction in transcatheter mitral valve-in-ring replacement and demonstrated a good agreement between the numerically predicted and CT-based measurements of the neo-LVOT area induced by the Sapien 3 device.

4. Verification, Validation, and Uncertainty Quantification

Regulatory agencies are currently considering the evidence obtained by modeling and simulations to reduce the time-to-market of biomedical devices as well as the cost related to the device design and animal trials. Therefore, given the lack of standardized modeling protocols, there is a growing interest in quantifying these models and to assess model credibility [60].

In this regard, the ASME published the V&V 40-2018 technical standard "Assessing Credibility of Computational Modeling through Verification and Validation: Application to Medical Devices", which introduced the model credibility evaluation process and provided the minimum requirements for qualification with respect to regulatory agencies.

Verification, validation, and uncertainty quantification (VVUQ) can be used to establish trust in the predictive capability of a given computational model. Verification assures that a computational model fits the mathematical description. Validation is performed to assess if the model accurately represents the real-world system for a defined application. Uncertainty quantification is implemented to determine the impact of numerical and physical parameter variations on the simulation outcome [61,62]. The ASME V&V 40-2018 standard proposes a risk-based framework for establishing the credibility requirements of computational modeling for a specific context of use, which defines the specific role and goal of the computer model to address a question. For a detailed understanding of ASME V&V 40, we recommend the article published by Viceconti and collaborators [60].

A few studies performed verification, validation, and uncertainty quantification (VVUQ) on cardiovascular problems. Luraghi and collaborators applied verification analysis for the simulation of an idealized tri-leaflet heart valve model by inspecting the impact of element type, formulation, and damping factor [63]. Similarly, Tango et al. validated an FSI model of the aortic valve and root by comparing the predicted velocity field with that of an in vitro flow analysis [64]. Recently, Bosi et al. [35] validated the computational modeling of TAVR with both Sapien XT and CoreValve devices against postprocedural clinical fluoroscopy and echocardiography images. They found good agreement between the predicted and image-based device diameters. A further step forward in CFD/FSI models of TAVR would be comparing the validation model to the experimental data, which is pivotal for enabling the full impact of these models on clinical interventions. In this regard, several in vitro approaches for arterial flow measurements (i.e., particle image velocimetry) have been identified as useful tools to validate fluid dynamic models [65]. An additional challenge is the VVUQ analysis for patient-specific geometries, as this is currently an area of intense regulatory science research linked to the development of a digital twin.

5. Future Directions

The success of TAVR and TMVR is continuously increasing as these procedures are applied to young patient cohorts and patients with a bicuspid anatomy of the aortic valve. Given the recent expansion of TAVR for low-risk severe AS and patients with bicuspid anatomy of the aortic valve, further efforts are needed to evaluate risk stratification and long-term device durability prior to implantation. Computational modeling represents a unique resource for the assessment of risk stratification, preprocedural planning and postprocedural care. Despite the growing accuracy of these predictive and simulation models, an important question remains open: can modeling and simulation be used in the regulatory process, thus reducing clinical trials and improving the time-to-market of a device application? Undoubtedly, additional investigations need to be performed to better evaluate the credibility of models, with the ultimate goal of using them in silico in daily clinical practice. Machine learning and 3D printing could be considered novel and complementary tools. Specifically, 3D printing could improve the assessment of TAVR- and TMVR-related anatomical suitability based on a direct and fast visualization of a patient's anatomy. Machine learning has demonstrated the potential to accurately predict long-term prognosis post-TAVR using advanced clinical metrics [66]. In this context, the artificial intelligence-derived risk model based on the acquirements of numerous input variables could enhance the high-dimensional model applicability in the future [67].

In conclusion, predictive computational models offer the potential to reveal the mechanisms of TAVI and TMVR whose implications cannot be easily determined by traditional imaging modalities. Combining statistical and structural/fluid dynamic models could greatly enhance the prediction of adverse events after TAVR and TMVR as well as improve the designing of next generation of THVs.

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